PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

# PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>04 April 2001 (04.04.01) | |
| **International application No.**<br>PCT/EP00/06504 | **Applicant's or agent's file reference**<br>HMR99L043/PCT |
| **International filing date** (day/month/year)<br>08 July 2000 (08.07.00) | **Priority date** (day/month/year)<br>21 July 1999 (21.07.99) |
| **Applicant**<br>BREIPOHL, Gerhard et al | |

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 February 2001 (15.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|---|
| **The International Bureau of WIPO**<br>**34, chemin des Colombettes**<br>**1211 Geneva 20, Switzerland** | Authorized officer<br>G. Bähr |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

146.1379

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Date of Deposit: January 11, 2002

I hereby certify that this correspondence is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" Service under 37 CFR 1.10 on the date indicated above and is addressed to Asst. Commissioner for Patents, Washington, D.C. 20231.

Charles A. Muserlian

# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

VIEILLEFOSSE, Jean Claude
Aventis Pharma S.A.
102, route de Noisy
93235 Romainville Cedex
FRANCE

# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

| Date of mailing *(day/month/year)* | 12.07.2001 |
|---|---|

| Applicant's or agent's file reference | IMPORTANT NOTIFICATION |
|---|---|
| HMR99L043/PCT | |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/EP00/06504 | 08/07/2000 | 21/07/1999 |

Applicant
AVENTIS PHARMA DEUTSCHLAND GMBH

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

| Name and mailing address of the IPEA/ | Authorized officer |
|---|---|
| European Patent Office<br>D-80298 Munich | Ambroa, J.R. |

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| HMR99L043/PCT | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/EP00/06504 | 08/07/2000 | 21/07/1999 |
| International Patent Classification (IPC) or national classification and IPC<br>C07D239/16 | | |
| Applicant<br>AVENTIS PHARMA DEUTSCHLAND GMBH | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 15/02/2001 | 12.07.2001 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Gettins, M<br>Telephone No. +49 89 2399 8273 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06504

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

1-31 as originally filed

**Claims, No.:**

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-10 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-10 |
| Industrial applicability (IA) | Yes: | Claims | 1-10 |
| | No: | Claims | |

2. Citations and explanations
**see separate sheet**

## VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
**see separate sheet**

1). Consistent nomenclature and names must be used throughout the current application. It should accordingly be made explicitly clear that: claim 6 is directed to the preparation of the compound (I) as defined in claim 1; that compounds (XV) represent a subset of compounds (II) and that claim 10 describes the conversion of (XIII) as described in claim 9 to (XV) as described in claim 7.

2). Relevant prior art is provided by:

(A) WO99/32457
(B) WO95/32710
(C) WO99/37621

(C) is an P document and, since the priority is valid, is not valid prior art for assessing novelty or inventive step during the PCT examination. An opinion is given as to why (C) is not novelty destroying as this may be relevant at the national phase. It is not relevant prior art for the assessment of inventive step.

3). The current application can be considered to be novel vis-à-vis (A) on account of the sulfonylamino group. It is considered to be a novel selection from (B). The compound claim 1 is novel vis-à-vis the structurally closest known compound (C), example 30, on account of the hemifurate group. The process claim 3 is novel vis-à-vis (C), example 30 on account of the starting materials (II) and (III).

4). On page 4, lines 24-32 the problem underlying the current application is defined as the provision of a suitable form of (IV) (i.e. a form which is easily isolated, purified and synthesised) which is said to be solved by the salt (I). It is not readily apparent which problem is solved by the compounds (IV) which are not the specific salt (I) i.e. which are the free form of (IV) or are salts other than the hemifurate salt. The Applicant is asked to either incorporate claim 6 into claim 3 or else indicate which problem is solved by the full scope of claim 3. It must be clear that a common problem exists which is solved by all of the claimed matter otherwise the question of unity needs to be resolved. It is further noted that the term "salt" in claim 3 is not precisely defined. Since this term is important for

the light of the description (acid salt?, base salt), organic salt?). Since no acids other than fumaric acid appear to be mentioned in the description it would be appropriate to limit the scope of claim 3 to the production of the compound (I). At present unity can be clearly observed in claims 1, 2, 3-5 (all partially), and 6-10. These claims all relate to (I) or to novel intermediates which can be directly converted to (I) without passing via previously known intermediates. Since the Applicant did not clarify this point claims 3-5 in so far as they do not refer to the production of (I) have not been examined.

An inventive step for the whole scope of the claims would presumably be linked to the properties of the hemifurate salt of (IV) (i.e. compound (I)) when compared with the closest prior art. Example 30 of (C) describes the same compound (IV), but as a hydrochloride salt instead of a hemifurate salt. On page 4, line 12 it is stated that example 30 from (C) cannot be isolated or purified by crystallisation or at least precipitation. It is further stated, page 4, lines 20-23 that various other acid salts cannot be crystallised or at least precipitated. The alleged advantages of the compound (I) i.e. improved ease of industrial synthesis and legally defined levels of purity are technically important, but are not in themselves grounds for acknowledging inventive step. It is further noted that there is no empirical data on file showing that salt forms other than hemifurate cannot be isolated or purified. This applies in particular to the hydrochloride salt known from (C). The Applicant would need to provided empirical data to support the allegations made Re the difficulty in obtaining salt forms of (IV). On page 19, the Applicant states that the process of the current application gives a better yield than would be obtained by the process in (C). Even if true, and at present this statement has not been made credible by means of empirical data, this would only be an indication of an inventive step for the process claims and not for the compound (IV). At present possible advantages have been listed vis-à-vis a specific compound, but these advantages have, not yet, been shown to really occur.

To summarise the Applicant could most easily demonstrate inventive step for current claims 3-10 by incorporating claim 6 into claim 3 and by showing that the hemifurate salt is more easily crystallised than the hydrochloride salt known from (C). This improved crystallisation would need to be made credible by means of empirical data. An inventive step for claims 1 and 2 would need to be shown by

means of an inventive improvement in properties. page 5, line 14 refers to improved non-hygroscopicity and stability. If this improvement can be shown an inventive step couldbe acknowledged for claims 1 and 2.

It is noted that (C) is not valid prior art for assessing inventive step. Since however the current application is a selection from (B) (i.e. structural overlap and same activity) an inventive step needs to be shown against (B). The structurally closest non-claimed and exemplified compound is found in (C), example 30. If an inventive step can be shown against this compound an inventive step vis-à-vis (B) could also be acknowledged. The Applicant could alternatively show an inventive step vis-à-vis (B) without a comparison against the compound known from (C). Any such comparison would need to be made credible on the basis of empirical data.

5). The Applicant has not given the patent publication number corresponding to EP99102916.6 or replaced PCT/EP99/00242 cited on several pages with WO99/37261. The reference on page 3, line 25 to WO97/23451 appears to be incorrect. The Applicant should clarify whether it should not in fact be a reference to WO97/23451.

# PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | FOR FURTHER ACTION | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
|---|---|---|
| HMR99L043/PCT | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/EP 00/ 06504 | 08/07/2000 | 21/07/1999 |

Applicant

AVENTIS PHARMA DEUTSCHLAND GMBH

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in th international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

1,4,5,6 -TETRAHYDROPYRIMIDINE DERIVATIVE AS A VITRONECTIN INHIBITOR

5. With regard to th **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/06504

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/16 A[redacted]1/505 C07D239/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | WO 99 37621 A (CUTHBERTSON ROBERT ANDREW ;SCHEUNEMANN KARLHEINZ (DE); KNOLLE JOCH) 29 July 1999 (1999-07-29) page 61 -page 62; example 30 | 1-10 |
| X | WO 95 32710 A (MERCK & CO INC ;HARTMAN GEORGE D (US); DUGGAN MARK E (US); IHLE NA) 7 December 1995 (1995-12-07) cited in the application claims 1,12 | 1 |
| A | WO 99 32457 A (CUTHBERTSON ROBERT ANDREW ;KNOLLE JOCHEN (DE); BREIPOHL GERHARD (D) 1 July 1999 (1999-07-01) cited in the application claim 1 | 1-10 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 October 2000 | 02/11/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 P.a. [illegible] 2 | |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/06504

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9937621 A | 29-07-1999 | AU 2518199 A | 09-08-1999 |
| | | NO 20003765 A | 25-09-2000 |
| WO 9532710 A | 07-12-1995 | AU 701776 B | 04-02-1999 |
| | | AU 2586895 A | 21-12-1995 |
| | | CA 2190870 A | 07-12-1995 |
| | | EP 0760658 A | 12-03-1997 |
| | | JP 10501222 T | 03-02-1998 |
| | | US 5929120 A | 27-07-1999 |
| | | US 5741796 A | 21-04-1998 |
| WO 9932457 A | 01-07-1999 | EP 0933367 A | 04-08-1999 |
| | | AU 2270099 A | 12-07-1999 |
| | | EP 1042301 A | 11-10-2000 |
| | | NO 20003118 A | 21-08-2000 |
| | | ZA 9811571 A | 21-06-1999 |

DL = 02-02-01

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

# PCT

To:
HOECHST MARION ROUSSEL
Attn. VIEILLEFOSSE, Jean C.
102, route de Noisy
93235 Romainville Cedex
FRANCE



NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

| | |
|---|---|
| Applicant's or agent's file reference<br>HMR99L043/PCT | Date of mailing *(day/month/year)*<br>02/11/2000 |
| International application No.<br>PCT/EP 00/ 06504 | **FOR FURTHER ACTION** See paragraphs 1 and 4 below |
| Applicant<br>AVENTIS PHARMA DEUTSCHLAND GMBH | International filing date *(day/month/year)*<br>08/07/2000 |

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

**For more detailed instructions,** see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

| | |
|---|---|
| Name and mailing address of the International Searching Authority<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Authorized officer<br>Véronique Baillou |

# NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Pat nt Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

## INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

**What parts of the international application may be amended?**

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

**When?** Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

**Where not to file the amendments?**

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

**How?** Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

**The amendments must be made in the language in which the international application is to be published.**

**What documents must/may accompany the amendments?**

**Letter (Section 205(b)):**

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

**The letter must be in English or French, at the choice of the applicant. However, if the language of th international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.**

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

**The following examples illustrate the manner in which amendments must be explained in the accompanying letter:**

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

**"Statement under article 19(1)" (Rule 46.4)**

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international appplication is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

**Consequence if a demand for international preliminary examination has already been filed**

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

**Consequence with regard to translation of the international application for entry into the national phase**

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

ATENT COOPERATION TREATY



# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| HMR99L043/PCT | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/EP00/06504 | 08/07/2000 | 21/07/1999 |
| International Patent Classification (IPC) or national classification and IPC<br>C07D239/16 | | |
| Applicant<br>AVENTIS PHARMA DEUTSCHLAND GMBH | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 15/02/2001 | 12.07.2001 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich | Authorized officer<br>Gettins, M |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06504

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

1-31 as originally filed

**Claims, No.:**

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-10 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-10 |
| Industrial applicability (IA) | Yes: | Claims | 1-10 |
| | No: | Claims | |

2. Citations and explanations
**see separate sheet**

## VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the [illegible] the description, are made:

1). Consistent nomenclature and names must be used throughout the current application. It should accordingly be made explicitly clear that: claim 6 is directed to the preparation of the compound (I) as defined in claim 1; that compounds (XV) represent a subset of compounds (II) and that claim 10 describes the conversion of (XIII) as described in claim 9 to (XV) as described in claim 7.

2). Relevant prior art is provided by:

(A) WO99/32457
(B) WO95/32710
(C) WO99/37621

(C) is an P document and, since the priority is valid, is not valid prior art for assessing novelty or inventive step during the PCT examination. An opinion is given as to why (C) is not novelty destroying as this may be relevant at the national phase. It is not relevant prior art for the assessment of inventive step.

3). The current application can be considered to be novel vis-à-vis (A) on account of the sulfonylamino group. It is considered to be a novel selection from (B). The compound claim 1 is novel vis-à-vis the structurally closest known compound (C), example 30, on account of the hemifurate group. The process claim 3 is novel vis-à-vis (C), example 30 on account of the starting materials (II) and (III).

4). On page 4, lines 24-32 the problem underlying the current application is defined as the provision of a suitable form of (IV) (i.e. a form which is easily isolated, purified and synthesised) which is said to be solved by the salt (I). It is not readily apparent which problem is solved by the compounds (IV) which are not the specific salt (I) i.e. which are the free form of (IV) or are salts other than the hemifurate salt. The Applicant is asked to either incorporate claim 6 into claim 3 or else indicate which problem is solved by the full scope of claim 3. It must be clear that a common problem exists which is solved by all of the claimed matter otherwise the question of unity needs to be resolved. It is further noted that the term "salt" in claim 3 is not precisely defined. Since this term is important for assessing unity and inventive step its precise scope needs to be clearly defined in

the light of the description (acid salt?, base salt), organic salt?). Since no acids other than fumaric acid appear to be mentioned in the description it would be appropriate to limit the scope of claim 3 to the production of the compound (I). At present unity can be clearly observed in claims 1, 2, 3-5 (all partially), and 6-10. These claims all relate to (I) or to novel intermediates which can be directly converted to (I) without passing via previously known intermediates. Since the Applicant did not clarify this point claims 3-5 in so far as they do not refer to the production of (I) have not been examined.

An inventive step for the whole scope of the claims would presumably be linked to the properties of the hemifurate salt of (IV) (i.e. compound (I)) when compared with the closest prior art. Example 30 of (C) describes the same compound (IV), but as a hydrochloride salt instead of a hemifurate salt. On page 4, line 12 it is stated that example 30 from (C) cannot be isolated or purified by crystallisation or at least precipitation. It is further stated, page 4, lines 20-23 that various other acid salts cannot be crystallised or at least precipitated. The alleged advantages of the compound (I) i.e. improved ease of industrial synthesis and legally defined levels of purity are technically important, but are not in themselves grounds for acknowledging inventive step. It is further noted that there is no empirical data on file showing that salt forms other than hemifurate cannot be isolated or purified. This applies in particular to the hydrochloride salt known from (C). The Applicant would need to provided empirical data to support the allegations made Re the difficulty in obtaining salt forms of (IV). On page 19, the Applicant states that the process of the current application gives a better yield than would be obtained by the process in (C). Even if true, and at present this statement has not been made credible by means of empirical data, this would only be an indication of an inventive step for the process claims and not for the compound (IV). At present possible advantages have been listed vis-à-vis a specific compound, but these advantages have, not yet, been shown to really occur.

To summarise the Applicant could most easily demonstrate inventive step for current claims 3-10 by incorporating claim 6 into claim 3 and by showing that the hemifurate salt is more easily crystallised than the hydrochloride salt known from (C). This improved crystallisation would need to be made credible by means of empirical data. An inventive step for claims 1 and 2 would need to be shown by

means of an inventive improvement in properties. page 5, line 14 refers to improved non-hygroscopicity and stability. If this improvement can be shown an inventive step couldbe acknowledged for claims 1 and 2.

It is noted that (C) is not valid prior art for assessing inventive step. Since however the current application is a selection from (B) (i.e. structural overlap and same activity) an inventive step needs to be shown against (B). The structurally closest non-claimed and exemplified compound is found in (C), example 30. If an inventive step can be shown against this compound an inventive step vis-à-vis (B) could also be acknowledged. The Applicant could alternatively show an inventive step vis-à-vis (B) without a comparison against the compound known from (C). Any such comparison would need to be made credible on the basis of empirical data.

5). The Applicant has not given the patent publication number corresponding to EP99102916.6 or replaced PCT/EP99/00242 cited on several pages with WO99/37261. The reference on page 3, line 25 to WO97/23451 appears to be incorrect. The Applicant should clarify whether it should not in fact be a reference to WO97/23451

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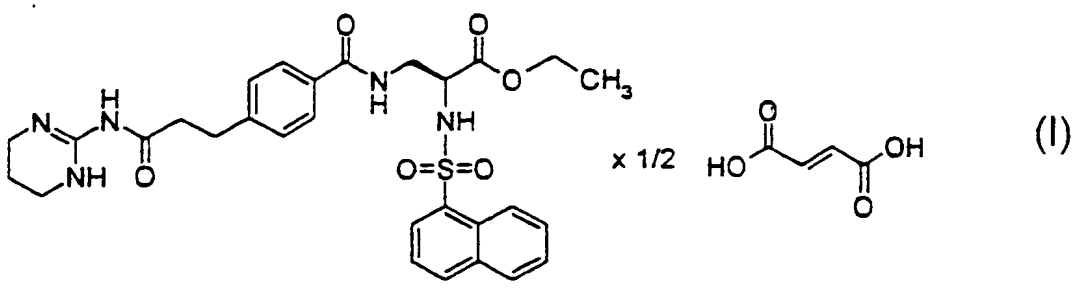
**Published:**
— *With international search report.*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: 1,4,5,6-TETRAHYDROPYRIMIDINE DERIVATIVE AS A VITRONECTIN INHIBITOR

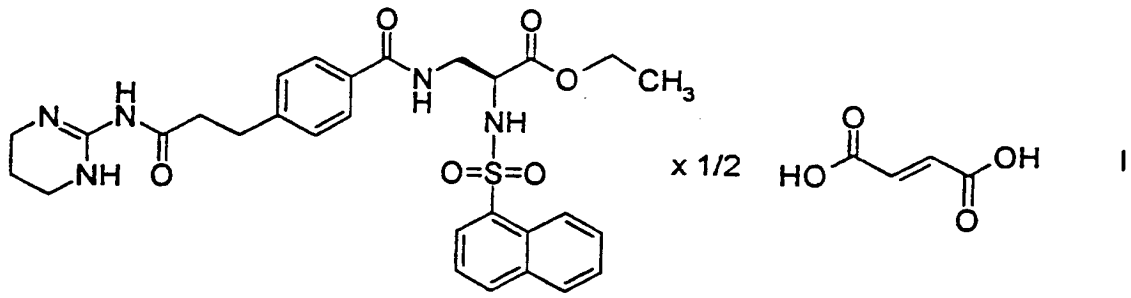



(57) Abstract: The present invention relates to ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate hemifumarate of formula (I), and to a process for its preparation comprising reacting 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid or a derivative thereof and ethyl (2S)-3-amino-2-(naphthalene-1-sulfonylamino)propionate. The compound of formula (I) is a valuable pharmaceutical which can be used, for example, in the treatment or prophylaxis of diseases which can be influenced by inhibiting the vitronectin receptor, in particular of bone diseases such as osteoporosis. The invention furthermore relates to chemical intermediates useful for the preparation of the compound of

WO 01/07417 A1

# 1,4,5,6 -TETRAHYDROPYRIMIDINE DERIVATIVE AS A VITRONECTIN INHIBITOR

The present invention relates to ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate hemifumarate of the formula I,




I

and to a process for its preparation comprising reacting 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid or a derivative thereof and ethyl (2S)-3-amino-2-(naphthalene-1-sulfonylamino)propionate. The compound of the formula I is a valuable pharmaceutical which can be used, for example, in the treatment or prophylaxis of diseases which can be influenced by inhibiting the vitronectin receptor, in particular of bone diseases such as osteoporosis. The invention furthermore relates to chemical intermediates useful for the preparation of the compound of formula I.

Bones are subject to an ongoing dynamic renovation process comprising bone resorption and bone formation. In certain bone diseases like osteoporosis bone resorption predominates over bone formation thus leading to lower bone mass and enhanced fragility. Bone resorption and bone formation are controlled by types of cell specialized for these purposes. Bone resorption is based on the destruction of bone

matrix by osteoclasts. Activated osteoclasts become attached to the surface of the bone matrix and secrete proteolytic enzymes and acids which cause the destruction of the bone. The attachment of osteoclasts to the bones, and thus bone resorption, is controlled by vitronectin receptors $\alpha_v\beta_3$ on the cell surface of osteoclasts. $\alpha_v\beta_3$ in this case binds to bone matrix proteins such as osteopontin, bone sialoprotein and thrombospontin. Antagonists of $\alpha_v\beta_3$ inhibit the attachment of osteoclasts to the bones and thus bone resorption as has been shown, for example, in in vivo experiments described by Fisher et al., Endocrinology 132 (1993) 1411; Yamamoto et al., Endocrinology 139 (1998) 1411; or Miller et al., Bioorg. Med. Chem. Letters 9 (1999) 1807.

The vitronectin receptor $\alpha_v\beta_3$ is a membrane glycoprotein belonging to the superfamily of integrin receptors, and besides on osteoclasts is expressed on the cell surface of other cells such as endothelial cells, cells of the vascular smooth musculature or tumor cells and controls interaction processes in which such cells are involved. In addition to inhibiting bone resorption $\alpha_v\beta_3$ antagonists are therefore capable of influencing other processes such as tumor growth and metastasis, arteriosclerosis, angiogenesis or inflammation, and in general $\alpha_v\beta_3$ antagonists are suitable for the therapy and prophylaxis of diseases which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing this interaction. $\alpha_v\beta_3$ as a therapeutic target and indications for $\alpha_v\beta_3$ antagonists are reviewed, for example, in Hillis et al., Clinical Science 91 (1996) 639; Engleman et al., Ann. Rep. Med. Chem. 31 (1996) 191; or Samanen et al., Current Pharm. Design 3 (1997) 545.

For example, it has been shown by Yue et al., Pharmacol. Rev. Commun. 10 (1998) 9; or Coleman et al., Circulation Res. 84 (1999) 1268, that $\alpha_v\beta_3$ antagonists inhibit the migration of vascular smooth muscle cells and reduce neointima formation which leads to arteriosclerosis and restenosis after angioplasty.

It has also been shown that the vitronectin receptor $\alpha_v\beta_3$ is involved in the progression of a variety of types of cancer, and that $\alpha_v\beta_3$ antagonists can cause a shrinkage of tumors by inducing the apoptosis of blood vessel cells during angiogenesis and can inhibit tumor growth and tumor metastasis (see, for example, Brooks et al., Cell 79 (1994) 1157; Carron et al., Cancer Res. 58 (1998) 1930; Yun et al., Cancer Res. 56 (1996) 1268; or above-mentioned references). The combination of $\alpha_v\beta_3$ antagonists with other known antitumor treatments has been shown to act highly efficiently on tumors and metastasis (see Lode et al., Proc. Natl. Acad. Sci. USA 96 (1999) 1591).

Friedlander et al., Science 270 (1995) 1500, have described $\alpha_v\beta_3$ antagonists which inhibit the bFGF-induced angiogenesis processes in the rat eye, a property which can be used therapeutically in the treatment of retinopathies and psoriasis. Storgard et al., J. Clin. Invest. 103 (1999) 47, have described the use of $\alpha_v\beta_3$ antagonists in the treatment of arthritic diseases.

Influencing the vitronectin receptor $\alpha_v\beta_3$ or the interactions in which it is involved thus offers the possibility of influencing different disease states for whose therapy and prophylaxis there continues to be a need for suitable pharmaceutical active ingredients .

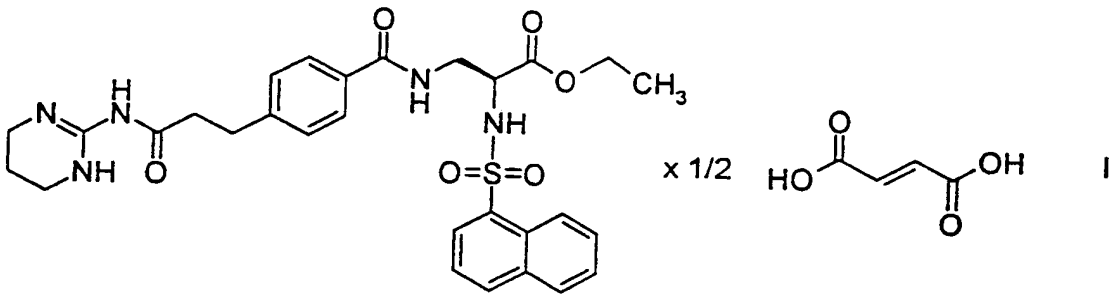
Various integrin antagonists including $\alpha_v\beta_3$ antagonists have already been described. Exemplarily there may be mentioned the compounds described in EP-A-820991, European Patent Application 99102916.6, WO-A-93/19046, WO-A-94/12181, WO-A-95/32710, WO-A-98/00395, WO-A-98/23451 or WO-A-99/32457. Certain sulfonamide derivatives which are particularly strong $\alpha_v\beta_3$ antagonists and inhibitors of bone resorption are described in International Patent Application PCT/EP99/00242 and its corresponding applications. Said sulfonamide derivatives include (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionic acid and esters thereof. Ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-

ylcarbamoyl)ethyl)benzoylamino)propionate which in vivo is hydrolyzed to the actually $\alpha_v\beta_3$ antagonistic (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionic acid, exhibits an especially favorable pharmacological profile.

By the process of preparation described in International Patent Application PCT/EP99/00242, the ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate is obtained as hydrochloride salt. However, it turned out that the hydrochloride salt which in the process of International Patent Application PCT/EP99/00242 is isolated by concentrating a solution of the free ester in hydrochloric acid and subsequently lyophilizing, cannot be isolated or purified by crystallization or at least precipitation. Consequently, the hydrochloride salt of ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate can scarcely be used as pharmacologically active drug substance in pharmaceuticals for whose constituents the legislator stipulates precisely defined degrees of purity, and as target product in an industrial synthesis as in the processes for preparing, isolating and purifying a drug substance likewise conditions and operating procedures have to be adhered to which are precisely defined by legal guidelines. Salts of ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate with various other acids, too, cannot be crystallized or at least precipitated, and they similarly could thus not be prepared on an industrial scale in a feasible, cost and labor effective manner. The object of the present invention is to provide ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate in a suitable form which allows an easy isolation and purification of the compound and which makes it possible to adhere with ease to the required degrees of purity and meet the demands associated with an industrial synthesis, as well as the galenic demands.

This object is achieved, surprisingly, by providing the hemifumarate salt of ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-

ylcarbamoyl)ethyl)benzoylamino)propionate which contains the ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate and fumaric acid in a molar ratio of 2:1 (or approximately 2:1), i. e. which contains 1/2 (= 0.5) (or approximately 1/2) mol of fumaric acid per mol of ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate. Thus, a subject of the present invention is ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate hemifumarate of the formula I.

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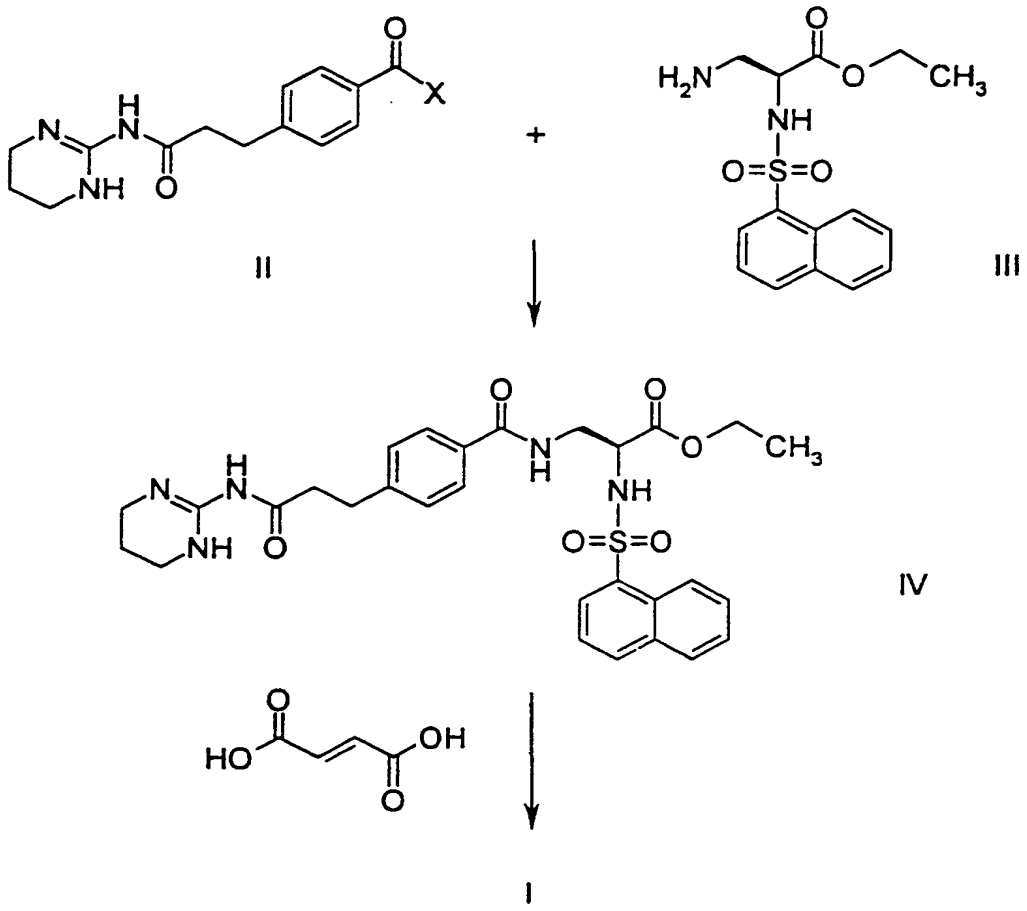
The specific salt of the formula I possesses advantageous physicochemical properties like non-hygroscopicity and stability which could not be foreseen. It can be easily isolated by precipitation, for example from the reaction solution obtained in the synthesis process, and if a purification is desired it can be precipitated under defined conditions, for example from a solution in ethanol. The compound thus fullfils the legal and technical demands on a drug substance.

The compound of the formula I can be prepared according to conventional procedures for the preparation of acid addition salts by combining the free ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate which may be obtained as an in situ intermediate as described in International Patent Application PCT/EP99/00242, with about 0.5 mol of fumaric acid per mol or an appropriate excess, for example about 0.55 or 0.6 mol of fumaric acid per mol, in a solvent or diluent, or it can be prepared

from another salt of ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate which may be obtained as an synthetic intermediate, by anion exchange. Preferably the compound of the formula I is prepared by a process which comprises a new synthetic strategy for the preparation of ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate, followed by conversion of the latter into the hemifumarate of the formula I. This new process which provides the desired compound by a simple convergent procedure in a high yield and which is outlined in the following, is another subject of the present invention.

The new process which allows the preparation of ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate of the formula IV and salts thereof, in particular of the hemifumarate of the formula I, is characterized by a condensation step in which 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid or a derivative thereof of the formula II and ethyl (2S)-3-amino-2-(naphthalene-1-sulfonylamino)propionate of the formula III, or a salt or salts of any one or both of these compounds, are reacted. The compound of the formula IV thus obtained can subsequently be converted into an acid addition salt by employing an acid, for example by employing fumaric acid for the preparation of the compound of the formula I.



The group COX in the compounds of the formula II can be the carboxylic acid group COOH or a reactive carboxylic acid derivative, for example a carboxylic acid halide such as the carboxylic acid chloride or the carboxylic acid bromide, a reactive carboxylic acid ester like an appropriate aryl ester such as the phenyl ester, the p-nitrophenyl ester or the pentafluorophenyl ester, a carboxylic acid azolide such as the imidazolide, or a group which usually is present only as an intermediate in solution like a mixed anhydride, for example a mixed carbonic acid anhydride obtained from the carboxylic acid and isobutyl chloroformate, or an activated ester like the 1-hydroxybenzotriazolyl ester or N-hydroxysuccinimidyl ester. X in the formula I thus can be hydroxy or a leaving group, for example, hydroxy, chlorine, bromine, unsubstituted or substituted phenyl, isobutoxycarbonyloxy, etc. Preferably X is hydroxy or chlorine, more preferably chlorine.

Salts as which the compounds of the formulae II and III may be employed in the reaction can be, for example, hydrohalides such as the hydrochloride or hydrobromide, salts with other inorganic acids like sulfuric acid, or salts with organic carboxylic acids or sulfonic acids like trifluoroacetic acid or p-toluenesulfonic acid. It may be advantageous to employ a compound of the formula II and/or a compound of the formula III in the form of a salt because in their preceding preparation the compounds of the formulae II and/or III are obtained as a salt and an additional step is to be avoided, and/or the salt can easier be handled in an industrial process, and/or the salt is more stable than the respective free compound. For example, if in the preceding preparation of the compound of the formula III the ethyl ester group is obtained from the respective carboxylic acid by esterification with ethanol in the presence of an acid like hydrogen chloride or sulfuric acid, the compound of the formula III is obtained as acid addition salt on the amine moiety with that acid, and moreover as such a salt the compound of the formula III is more stable during storage than the free amine. Similarly the compound of the formula II in which X is chlorine, for example, may be obtained in its preceding preparation in the form of the hydrochloride salt of the guanidine moiety, and as such a salt may be more stable and easier to handle. Preferably the compound of the formula III is employed in the reaction with the compound of the formula II as a salt, in particular as the hydrochloride salt. In case X is chlorine or bromine the compound of the formula II, too, is preferably employed as the respective hydrohalide salt, for example as the hydrochloride salt. In case X is hydroxy the compound of the formula II may be present as an inner salt (or betaine or zwitterion) containing a negatively charged carboxylate group and a positively charged guanidinium group, which type of salt is also included in the present invention.

The reaction of the compounds of the formulae II and III to give the compound of the formula IV is performed under usual conditions for the formation of an amide from an amine and a carboxylic acid or a derivative thereof which are well known to one skilled in the art, including the methods and conditions known from peptide chemistry. Details of such reactions can be found in standard references like

Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, 1974; or J. March, Advanced Organic Chemistry, Third Edition, John Wiley & Sons, 1985.

When the compound of the formula II in which COX is COOH is employed in the reaction it is usually first activated in situ with a common activating agent for carboxylic acids such as, for example, a carbodiimide like N,N'-dicyclohexylcarbodiimide or N,N'-diisopropylcarbodiimide, a uronium salt like O-((cyano(ethoxycarbonyl)methylen)amino)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU) or O-(7-azabenzotriazol-1-y)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), or propyl phosphonic anhydride. The activation can also be carried out to give as an in situ intermediate one of the compounds of the formula II already mentioned above, for example an imidazolide by reaction with 1,1'-carbonyldiimidazole, or a mixed carbonic acid anhydride by reaction with an alkyl chloroformate, or an acid halide like the acid chloride by reaction with a chlorinating agent such as thionyl chloride or oxalyl chloride. The activation can be performed under standard conditions. For example, the activation with an alkyl chloroformate, a carbodiimide or a uronium salt is usually carried out in an inert aprotic solvent, for example a hydrocarbon or chlorinated hydrocarbon like toluene or dichloromethane, an ether like tetrahydrofuran, dioxane or dimethoxyethan, an ester like ethyl acetate, an amide like N,N-dimethylformamide or N-methylpyrrolidone or a nitrile like acetonitrile, or a mixture of such solvents, at temperatures from about -10°C to about room temperature. The activated carboxylic acid is then reacted with the compound of the formula III, usually at temperatures from about -10°C to about room temperature. Usually the activation and the subsequent reaction with the compound of the formula III are carried out in the presence of a base like, for example, a tertiary amine such as triethylamine, N,N-diisopropylethylamine or N-methylmorpholine which base also liberates the free amine of the formula III in case a salt thereof is employed, and ensures that finally the free compound of the formula IV is present. The mentioned bases and solvents like the mentioned hydrocarbons, ethers, amide or nitriles may also be used when a compound of the formula II in which COX is a

such a reaction usually being carried out at temperatures from about 0°C to about 80°C.

When a compound of the formula II is employed in which X is chlorine or bromine, in particular chlorine, besides in solvents like hydrocarbons or chlorinated hydrocarbons such as toluene, chloroform or dichloromethane, ethers such as tetrahydrofuran, dioxane or dimethoxyethan, esters such as ethyl acetate, amides like N,N-dimethylformamide or N-methylpyrrolidone or nitriles such as acetonitrile, or mixtures of such solvents, the reaction can also be carried out in water or a mixture of one or more of the mentioned solvents and water, and particularly favorably it is carried out in a two phase system of water and an organic solvent which is substantially immiscible with water, for example in a mixture of a hydrocarbon or chlorinated hydrocarbon, for example dichloromethane, and water or in a mixture of an ester, for example ethyl acetate, and water.

In order to obtain the free compound of the formula IV a compound of the formula II in which X is chlorine or bromine is usually reacted with a compound of the formula III in the presence of a sufficient amount of a base which scavenges the hydrogen halide that is produced in the reaction, and which also liberates the free amine in case a salt of the compound of the formula III is employed. Besides tertiary amines like, for example, triethylamine or pyridine also inorganic bases can favorably be used, for example hydrogen carbonates like sodium hydrogen carbonate or potassium hydrogen carbonate, carbonates like lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, magnesium carbonate or calcium carbonate, or hydroxides like sodium hydroxide, potassium hydroxide or calcium hydroxide, or mixtures of such bases. In particular when the reaction is carried out in the presence of water the use of an inorganic base is preferred. Depending on the intended technical details of a reaction of a compound the formula II in which X is chlorine or bromine with a compound of the formula III, certain bases and certain modes of introducing the base into the reaction mixture are particularly advantageous. For example, in case a hydrogen carbonate is to be used in a two

beginning whereas in case a hydroxide is to be used it may be preferred to add the base gradually during the course of the reaction. It may also be favorable to add the base in such a manner that a certain pH range, for example a pH from about 5 to about 10, in particular from about 7 to about 9, is maintained during the reaction of a compound of the formula II in which X is chlorine or bromine with a compound of the formula III.

The reaction of a compound of the formula II in which X is chlorine or bromine with a compound of the formula III is usually carried out at temperatures from about 0°C to about 40°C, preferably at temperatures from about 10°C to about 30°C, in particular at about room temperature.

In general, depending on the specific mode of reaction the molar ratio of the compounds of the formulae II and III is usually from about 1.1:1 to about 1:1.1, preferably about 1:1. The compound of the formula II can be initially introduced, in particular if the compound of the formula II is employed in which X is hydroxy and which first is to be activated, and the compound of the formula III subsequently be added in one or several portions or continuosly. Just so, the compound of the formula III can be initially introduced and the compound of the formula II can be added in one or several portions or continously, or both components can also be metered simultaneously into the reaction vessel. The compounds of the formulae II and III can be employed in the form of solutions or suspensions or as solids. Depending on the details of the reaction, the reaction of the compounds of the formulae II and III is usually complete soon after mixing of the reactive components, and stirring of the reaction mixture usually needs to be continued not longer than for a few hours, for example 0.5 to 8 hours.

The workup of the reaction mixture depends on the specific manner in which the reaction is performed. In general, workup can be carried out using conventional working steps like adding water and/or organic solvents, adjusting the pH, separating phases, performing extractions, washing, drying, filtering, evaporating, etc. In case

the reaction of the compounds of the formula I is carried out in a water-immiscible organic solvent workup is preferably performed by adding water to give a two phase system, optionally adjusting a slightly basic pH, separating the phases, optionally extracting the aqueous phase, drying and optionally concentrating or evaporating the organic phases. In an according manner the workup is preferably performed in case the reaction is carried out in a mixture of a water-immiscible solvent and water. In case the reaction is carried out in a water-miscible organic solvent the workup is preferably performed by first removing the solvent under reduced pressure, then adding a water-immiscible solvent and water to give a two phase system and proceeding as before. In all these preferred workup procedures the free compound of the formula IV is directly obtained in the form of a solution in an organic solvent or, if in the evaporating step the solvent is completely removed, in the form of an evaporation residue which can then be dissolved in a desired organic solvent.

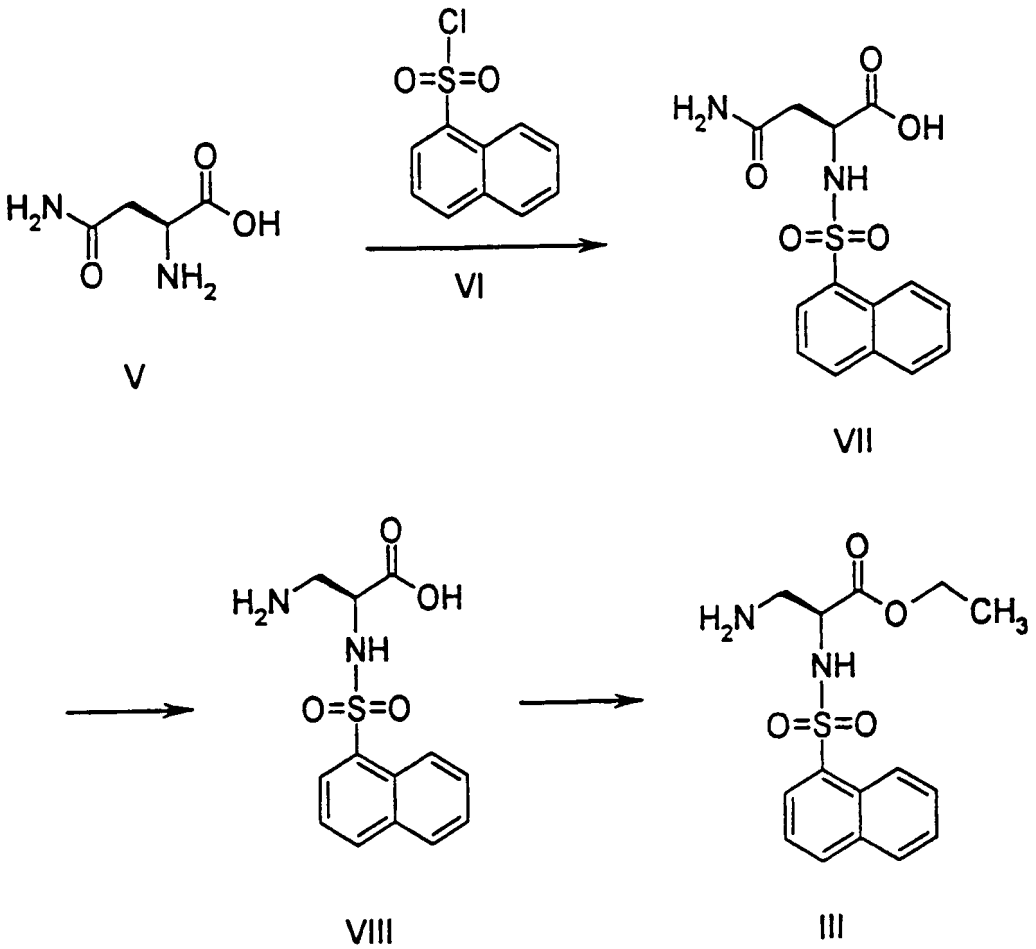
For the preparation of a desired acid addition salt of the compound of the formula IV the obtained solution of the compound of the formula IV is combined with the desired acid. The acid can be employed in pure form or in the form of a solution or suspension, and either the acid can be added to the solution of the compound of the formula IV, or the solution of the compound of the formula IV can be added to the acid. The preferred amount of the acid depends on the details of the specific salt formation. In case a 1:1 acid addition salt is to be prepared the acid is usually employed in a molar ratio of about 1:1 or in a molar excess from about 1.3:1 to 1:1 or from about 1.1:1 to 1:1 where usually the molar amount of the acid can conveniently be based on the molar amount of the starting compounds of the formulae II or III. In case a 2:1 acid addition salt containing two mol of the compound of the formula I per mol of acid is to be prepared the acid is usually employed in a molar ratio of about 0.5:1 (i. e. 0.5 mol of the acid per 1 mol of the compound of the formula IV) or in a molar excess from about 0.65:1 to 0.5:1 or from about 0.55:1 to 0.5:1. If the resulting salt cannot be crystallized or precipitated from the solution it is isolated by evaporation or lyophilization, and if desired the product is then subjected to purification procedures. If the salt crystallizes or can be precipitated the solvent in which the salt formation is carried out, the amount of the solvent and the temperature

are preferably chosen such that the crystallization or precipitation of the product starts from a clear solution.

In case the hemifumarate of the compound of the fomula IV, i. e. the compound of the formula I, is to be prepared preferably about 0.5 mol of fumaric acid, conveniently based on the molar amount of the starting compounds of the formula II or III, is added to the obtained solution of the compound of the formula IV, for example directly to its dried and partially evaporated solution in dichloromethane if this solvent is used for the reaction of the compounds of the formulae II and III and/or for extractive workup. After combining the fumaric acid and the compound of the formula IV it may be favorable first to heat the mixture to give a clear solution, for example to about 30°C to 40°C if dichloromethane is used, from which solution upon cooling the compound of the formula I starts to precipitate or can be precipitated. To complete precipitation the suspension may be cooled, for example to a temperature from about -10°C to about 5°C or a temperature from about -5°C to about 0°C, and/or an additional solvent may be added in which the salt is only slightly soluble. The solid hemifumarate of the formula I is then separated by filtration or centrifugation, washed, and if desired dried and/or purified. The product is obtained in high yield and high purity.

The starting compounds of the formulae II and III employed in the above reaction can be obtained as described in the following. The preparation of the ethyl (2S)-3-amino-2-(naphthalene-1-sulfonylamino)propionate of the formula III or a salt thereof may start from (S)-asparagine (= (L)-asparagine) of the formula V which is readily available in optically pure form. In the compound of the formula V the amino group is first sulfonylated under standard conditions with a reactive derivative of naphthalene-1-sulfonic acid, for example with naphthalene-1-sulfonyl chloride of the formula VI, usually in the presence of a base at temperatures from about 0°C to about room temperature. This reaction may conveniently be carried out, for example, in a mixture of an organic solvent and water, for example a mixture of tetrahydrofuran and water or of dimethoxyethane and water, using an alkali metal hydroxide as base, for example sodium hydroxide, with maintaining the pH in the alkaline range, for

example at about 12. The components can usually be employed in a molar ratio of about 1:1.

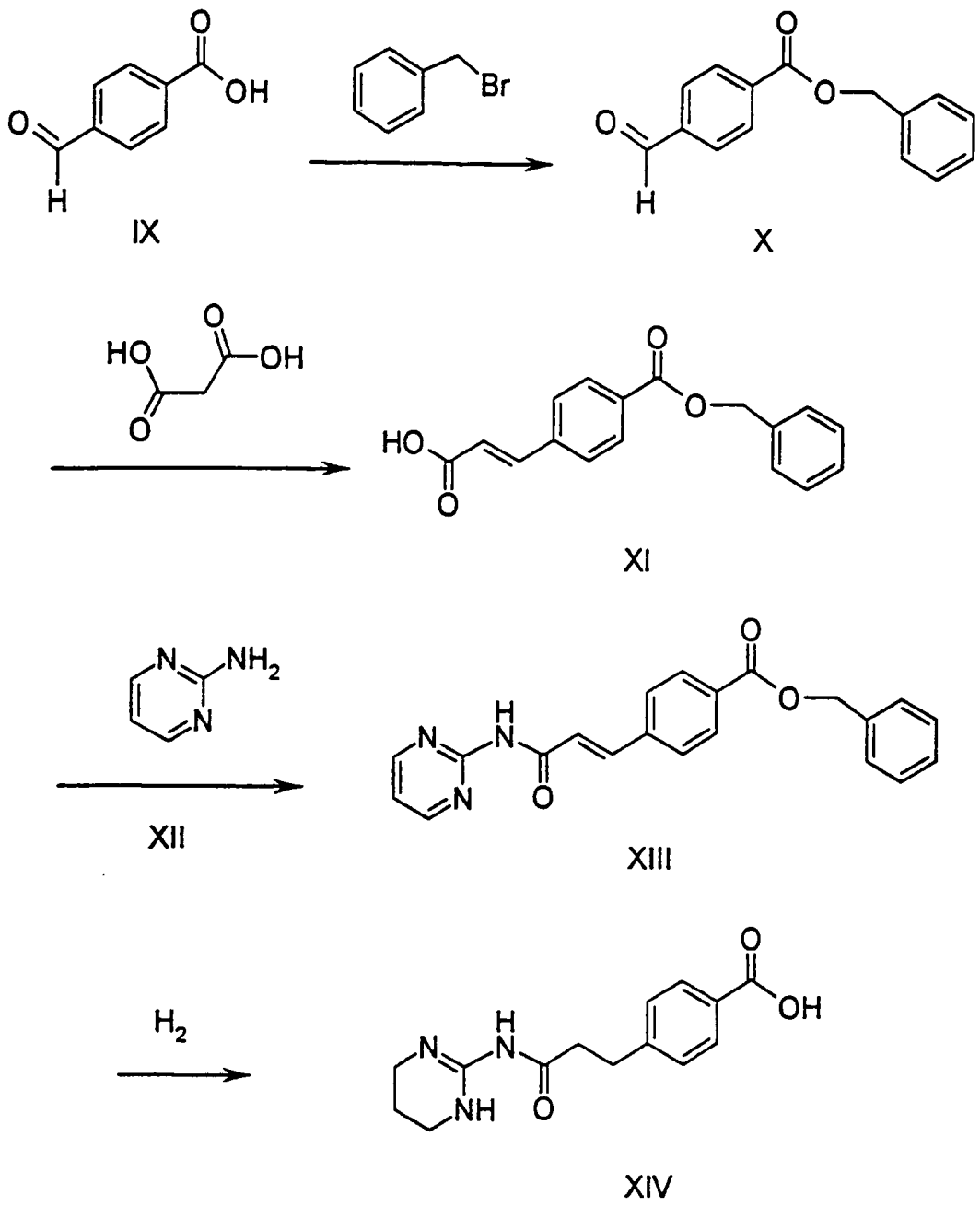



The carbamoyl group in the obtained succinamic acid derivative of the formula VII can then be converted into an amino group to give the 3-aminopropionic acid derivative of the formula VIII by means of a Hofmann degradation, i. e. by the action of a solution of chlorine or bromine in aqueous alkali metal hydroxide, for example sodium hydroxide or potassium hydroxide, or of an alkali metal hypohalite which is the active ingredient in such a solution. In detail the Hofmann degradation is preferably carried out substantially as described below in the example section using bromine and sodium hydroxide, following the method described by Amato et al., J. Org. Chem. 63 (1998) 9533. The product of the formula VIII may conveniently be isolated from the aqueous reaction mixture by acidification to a pH of about 6.5 to 7

Esterification of the compound of the formula VIII to give the compound of the formula II or a salt thereof can be carried out under standard conditions, for example with ethanol in the presence of an acid catalyst like gaseous hydrogen chloride or sulfuric acid at temperatures from about 20°C to the boiling temperature of ethanol. Preferably in the acidic esterification process more than one equivalent of the acid is employed so that the resulting aminoester of the formula VIII is present as the respective acid addition salt which can easily be isolated and exhibits a higher storage stability. Preferably the esterification is done by passing hydrogen chloride gas into a suspension of the compound of the formula VII in ethanol and isolating the product in the form of the hydrochloride of the compound of the formula VIII.

The preparation of the 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid or derivative thereof of the formula II or a salt thereof may start from commercially available 4-formylbenzoic acid of the formula IX. Under standard conditions as described, for example, by Hu et al., Bioorg. Med. Chem. 5 (1997) 1873 the acid of the formula IX is first converted into an appropriate ester, for example with a benzyl halide like benzyl bromide into the known benzyl ester of the formula X. To achieve such an O-alkylation usually the acid and the benzyl halide are reacted in a solvent or diluent, for example in an amide like N,N-dimethylformamide, in the presence of a base like, for example, potassium carbonate at room temperature or elevated temperature. The benzyl ester of the formula X can be directly used in the subsequent step in crude form without further purification.

The ester of the formula X is then condensed with malonic acid under the conditions of the Knoevenagel reaction to give the cinnamic acid derivative of the formula XI. When carried out under the classic conditions of the Knoevenagel condensation in pyridine in the presence of piperidine under reflux the yield of the resulting compound




To allow a smooth reaction with 2-aminopyrimidine of the formula XII to give the benzyl 4-(2-(pyrimidin-2-ylcarbamoyl)vinyl)benzoate of the formula XIII, the carboxylic acid moiety in the compound of the formula XII is expediently first activated or converted into a more reactive carboxylic acid derivative. The above explanations with regard to the activation of the carboxylic acid of the formula II in which X is hydroxy correspondingly apply to the activation of the compound of the formula XI. In a preferred manner, the compound of the formula XI is converted into

formula XI in which the group COOH is replaced with the group COCl, with a chlorinating agent such as thionyl chloride or oxalyl chloride under standard conditions. The acid of the formula XI may be reacted, for example, with an excess of thionyl chloride, if desired in an inert solvent like a hydrocarbon or chlorinated hydrocarbon such as toluene, until the evolution of sulfur dioxide and hydrogen chloride ceases. Following removal of the solvent and/or the excess thionyl chloride, the crude acid chloride (or another reactive derivative of the compound of the formula XI that is employed instead of the acid chloride) is then reacted with 2-aminopyrimidine under conventional conditions for the formation of an amide. The above explanations with regard to the reaction of the compounds of the formulae II and III correspondingly apply to the present reaction. Usually the reaction is carried out in the presence of a base, in the present case in particular a tertiary amine like triethylamine or preferably pyridine, in an inert solvent or diluent such as, for example, a hydrocarbon or chlorinated hydrocarbon like dichloromethane or an ether or ester at temperatures from about -10°C to about 20°C.

In the obtained compound of the formula XIII then the carbon carbon double bond in the CH=CH-CO-N moiety is reduced to a single bond, the heteroaromatic pyrimidin-2-yl moiety is reduced to a 1,4,5,6-tetrahydropyrimidin-2-yl moiety and the benzyl ester group is cleaved to give the 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid of the formula XIV. These three conversions can be achieved simultaneously in a single reaction step, namely by a catalytic hydrogenation. It is therefore preferred to proceed in the synthetic strategy of the present invention via the benzyl ester compounds of the formulae X, XI and XIII and perform the conversion of the compound of the formula XIII into the compound of the formula XIV including ester cleavage by catalytic hydrogenation.

The catalytic hydrogenation of the compound of the formula XIII or a salt thereof to the compound of the formula XIV is preferably carried out in the presence of a conventional noble metal catalyst, for example a palladium, rhodium or platinum catalyst, in particular in the presence of palladium on charcoal. The amount of the

be, for example, 0.5 to 5 mol-% (based on the compound of the formula XIII). As solvent or diluent one or more solvents like acetic acid, ($C_1$-$C_4$)-alcohols such as methanol, ethanol or isopropanol, in particular isopropanol, ethers such as tetrahydrofuran or dioxane, or water may be used, for example a mixture of acetic acid with one of the solvents water, isopropanol and dioxane, in particular a mixture of acetic acid and water. It is preferred to carry out the hydrogenation of the compound of the formula XIII at an acidic pH in the presence of a carboxylic acid like acetic acid which may also function as a solvent, or an inorganic acid like hydrochloric acid or sulfuric acid. Preferably a weak acid like acetic acid is employed. The choice of the hydrogen pressure depends on the available technical equipment and can be about 1 bar, or up to about 2 bar, or up to about 5 bar, or higher. The hydrogenation is usually carried out at temperatures from about 20°C to about 60°C. After removal of the catalyst the product of the formula XIV (which also is the compound of the formula II in which X is hydroxy) is isolated by conventional methods. In case the hydrogenation is carried in the presence of a strong acid like hydrochloric acid or sulfuric acid preferably the product is completely converted into the respective acid addition salt of the compound of the formula XIV, or the acid is neutralized and the product is completely converted into the free compound of the formula XIV (which may be an inner salt).

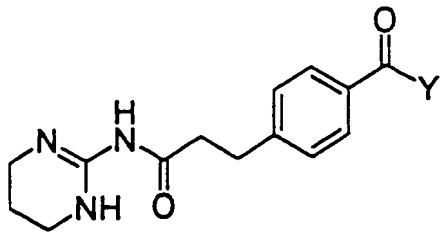
For the preparation of a compound of the formula II in which X is chlorine or bromine the compound of the formula XIV is converted into the carboxylic acid halide by a conventional chlorinating agent, for example thionyl chloride, oxalyl chloride or oxalyl bromide. Preferably the compound of the formula XIV is converted into the acid chloride, i. e. the compound of the formula II in which X is chlorine, by reaction with an excess of thionyl chloride, for example 1.2 to 2 mol thionyl chloride per mol of the compound of the formula XIV. An excess of thionyl chloride may also be used as solvent or diluent, or an inert solvent or diluent like a hydrocarbon or a chlorinated hydrocarbon such as toluene or dichloromethane may be added which, together with the excess thionyl chloride, after completion of the reaction is removed in vacuo. The reaction is usually carried out at elevated temperatures from about 40°C to about 100°C. The hydrogen halide that is formed during the transformation of the

compound of the formula XIV into an acid halide is bound by the basic guanidine moiety in the molecule to give the hydrogen halide addition salt. The acid halide is preferably isolated in the form its solid hydrogen halide salt which can directly be employed in the reaction with the compound of the formula III as explained above.

As a whole, the above-described process for the preparation of the compound of the formula I from the compounds of the formulae II and III, taken together with the above-described processes for the preparation of the starting compounds of the formulae II and III, provides the compound of the formula I in a simple manner and in an exceptional high overall yield from readily available starting materials. Among the potential strategies for building the molecule of the formula I (or the formula IV) the unique way in which in the present process small building blocks are assembled to certain intermediates which are then combined to give the final target compound, thus proves to be particularly successful. At any rate the yield obtained in the present process is considerably higher than the yield of the compound of the formula I that would be obtainable if the process of International Patent Application PCT/EP99/00242 would be followed for the preaparation of the intermediate compound of the formula IV, and the present process is simpler and better applicable on an industrial scale than that of International Patent Application PCT/EP99/00242. To a considerable amount the advantages of the present process are based on the use of the key intermediates of the formulae II and XIV, i. e. on the use of 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid and its derivatives, and on the favorable process for their preparation, in particular the simple preparation of the compound of the formula XIV by hydrogenation of its precursor of the formula XIII which in one step accomplishes the removal of the benzoic acid benzyl protection group and the reduction of as well the cinnamic acid double bond as the pyrimidine ring.

A subject of the present invention are therefore also the compounds the formulae II and XIV which are valuable intermediates for the preparation of pharmacologically active compounds like the hemifumarate of the formula I or other salts of the compound of the formula IV, or of other compounds which contain a 4-(2-(1,4,5,6-

tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoyl moiety. A subject of the present invention are in particular the compounds of the formula XV,



XV

in which Y is hydroxy, chlorine or bromine, and their salts. Examples of salts of the compounds of the formula XV are hydrogen chloride salts or hydrogen bromide salts which may in particular be present in case Y is chlorine or bromine. The compound of the formula XV in which Y is hydroxy and which is not an acid addition salt at the guanidine moiety is also covered by the formula XV and by the present invention as an inner salt (or betaine). Preferred compounds of the formula XV are those compounds in which Y is hydroxy or chlorine, and the salts thereof, i. e. 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid and 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoyl chloride and their salts, in particular the hydrochloride salt in the case of the compound of the formula XV in which Y is chlorine. Further subjects of the present invention are the above-described exceptionally simple and highly efficient process for the preparation of 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid or a salt thereof by hydrogenation of benzyl 4-(2-(pyrimidin-2-ylcarbamoyl)vinyl)benzoate or a salt thereof, as well as benzyl 4-(2-(pyrimidin-2-ylcarbamoyl)vinyl)benzoate of the formula XIII or a salt thereof which is the starting material for said process.

The compound of the formula I is a valuable pharmacologically active compound which is suitable, for example, for the therapy and prophylaxis of bone disorders, tumor diseases, cardiovascular disorders or inflammatory conditions. The compound of the formula I can be administered to animals, preferably to mammals, and in particular to humans as a pharmaceutical for therapy or prophylaxis. It can be

or in the form of pharmaceutical compositions which permit enteral or parenteral administration and which, as active constituent, contain an efficacious dose of the compound of the formula I.

The present invention therefore also relates to the compound of the formula I for use as a pharmaceutical, to the use of the compound of the formula I for the production of pharmaceuticals for the therapy and prophylaxis of the diseases mentioned above or below, for example for the therapy and prophylaxis of bone disorders, and also to the use of the compound of the formula I for the therapy and prophylaxis of these diseases and to methods for such therapy and prophylaxis. The present invention furthermore relates to pharmaceutical compositions (or pharmaceutical preparations) which contain an efficacious dose of the compound of the formula I and a customary pharmaceutically acceptable carrier, i. e. one or more pharmaceutically acceptable carrier substances and/or additives.

The pharmaceuticals can be administered orally, for example in the form of pills, tablets, lacquered tablets, coated tablets, granules, hard and soft gelatin capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injection solutions or infusion solutions, microcapsules, implants or rods, or percutaneously or topically, for example in the form of ointments, solutions emulsions or tinctures, or in other ways, for example in the form of aerosols or nasal sprays.

The pharmaceutical compositions according to the invention are prepared in a manner known per se and familiar to those skilled in the art, the compound of the formula I being mixed with one or more pharmaceutically acceptable inert inorganic and/or organic carrier substances (or excipients) and/or additives and, if desired, one or more other pharmaceutically active compounds and being brought into a suitable administration form and dosage form that can be used in human or veterinary medicine. For the production of pills, tablets, coated tablets and hard gelatin capsules

stearic acid or its salts, etc. Carrier substances for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carrier substances for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, alcohols, glycerol, polyols, sucrose, invert sugar, glucose, vegetable oils, etc. Suitable carrier substances for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid. The pharmaceutical compositions normally contain about 0.5 to 90 % by weight of the compound of the formula I. The amount of the active ingredient of the formula I in the pharmaceutical compositions normally is from about 0.2 mg to about 500 mg, preferably from about 1 mg to about 200 mg but depending on the type of the pharmaceutical composition it may also be higher.

In addition to the active ingredient of the formula I and carrier substances, the pharmaceutical compositions can contain additives (or auxiliary substances) such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants. Furthermore, in addition the compound of the formula I, they can also contain one or more other therapeutically or prophylactically active ingredients.

The compound of the formula I in vivo is an antagonist of the vitronectin receptor and inhibits cell adhesion. It has, for example, the ability to inhibit the binding of osteoclasts to the bone surface and thereby inhibit bone resorption by osteoclasts. The action of the compound of the formula I can be demonstrated, for example, in the test described below. Because of its vitronectin receptor antagonistic activity the compound of the formula I is generally suitable for the therapy and prophylaxis of diseases which are based on the interaction between vitronectin receptors and their ligands in cell-cell interaction processes or cell-matrix interaction processes, or which can be influenced by an inhibition of interactions of this type, or for the prevention, alleviation or cure of which an inhibition of interactions of this type is desired. As

explained at the beginning, such interactions play a part, for example, in bone resorption, in angiogenesis or in the proliferation of cells of the vascular smooth musculature. The compound of the formula I is therefore suitable, for example, for the prevention, alleviation or cure of diseases which are caused at least partially by an undesired extent of bone resorption, angiogenesis or proliferation of cells of the vascular smooth musculature.

Bone diseases for whose treatment and prevention the compound of the formula I can be employed are especially osteoporosis, hypercalcemia, osteopenia, for example caused by metastases, dental disorders, hyperparathyroidism, periarticular erosions in rheumatoid arthritis and Paget's disease. In addition, the compound of the formula I can be used for the allevation, avoidance or therapy of bone disorders which are caused by a glucocorticoid, steroid or corticosteroid therapy or by a lack of sex hormone(s). All these disorders are characterized by bone loss which is based on the inequilibrium between bone formation and bone destruction and which can be favorably influenced by the inhibition of bone resorption by osteoclasts. The compound of the formula I can also favorably be used as inhibitor of bone resorption, for example in the therapy or prophylaxis of osteoporosis, in combination with conventional osteoporosis treatments such as, for example the administration of bisphosphonates, estrogens, estrogen/progesterone (hormone replacement therapy or HRT), estrogen agonists/antagonists (selective estrogen receptor modulators or SERMs), calcitonin, vitamin D analogues, parathyroid hormone, growth hormone secretagogues, or sodium fluoride (cf. Jardine et al., Annual Reports in Medicinal Chemistry 31 (1996) 211). Administration of the compound of the formula I and of other active ingredients effective in the treatment or prophylaxis of osteoporosis like those listed before can take place simultaneously or sequentially, in any order, and jointly or separately. For use in such a combination treatment or prophylaxis the compound of the formula I and one or more other active ingredients like those listed before can together be present in a single pharmaceutical composition, for example tablets, capsules or granules, or can be present in two or more separate pharmaceutical compositions which can be contained in a single package or in two or

combination therapy or prophylaxis and their use in the production of pharmaceuticals for such a combination therapy or prophylaxis are also subjects of the present invention. The invention furthermore relates to pharmaceutical compositions which comprise an efficacious amount of the compound of the formula I together with at least one other active ingredient effective in the treatment or prophylaxis of osteoporosis or in the inhibition of bone resorption like those listed before, together with a customary pharmaceutically acceptable carrier. The above explanations on pharmaceutical compositions correspondingly apply to such pharmaceutical combination compositions.

Apart from use as inhibitors of bone resorption by osteoclasts, the compound of the formula I can be used, for example, as inhibitors of tumor growth and tumor metastasis, as antiinflammatories, for the therapy or prophylaxis of rheumatoid arthritis, for the therapy of psoriasis, for the therapy or prophylaxis of cardiovascular disorders such as arteriosclerosis or restenoses, for the therapy or prophylaxis of nephropathies or retinopathies such as, for example, diabetic retinopathy. As inhibitor of tumor growth or tumor metastasis the compound of the formula I can also favorably be used in combination with conventional cancer therapy. Examples of conventional cancer therapy are given in Bertino (Editor), Encyclopedia of Cancer, Academic Press, 1997 which is incorporated herein by reference. All the above statements relating to the use of the compound of formula I in combination with conventional osteoporosis therapy like, for example, possible modes of administration and pharmaceutical combination compositions, correspondingly apply to the use of the compound of formula I in combination with conventional cancer therapy.

When using the compound of the formula I, the dose can vary within wide limits and, as is customary, is to be suited to the individual conditions in each individual case. It depends, for example, on the nature and severity of the disease and the general state of the individual to be treated, or on whether an acute or chronic condition is treated or whether prophylaxis is carried out. In the case of oral administration, the daily dose is in general from about 0.01 to about 100 mg/kg, preferably from about

0.1 to about 50 mg/kg, in particular from about 0.1 to about 5 mg/kg, to achieve effective results in an adult weighing about 75 kg (in each case in mg per kg of body weight). Also in the case of intravenous administration the daily dose is in general from about 0.01 to about 100 mg/kg, preferably from about 0.05 to about 10 mg/kg (in each case in mg per kg of body weight). The daily dose can be divided, in particular in the case of the administration of relatively large amounts, into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behavior it may be necessary to deviate upwards or downwards from the daily dose indicated.

The compound of the formula I can furthermore be employed for diagnostic purposes or as auxiliary in pharmacological or biochemical investigations in which blocking of the vitronectin receptor or influencing of cell-cell or cell-matrix interactions is desired.

Examples

1) 4-Benzyloxycarbonylcinnamic acid

a) Benzyl 4-formylbenzoate

304 g (2 mol) of 4-formylbenzoic acid were dissolved in 1 l of dimethylformamide (DMF), 304 g (2.2 mol) of potassium carbonate were added and then over a period of 30 min 261 ml (2.2 mol) of benzyl bromide were added at about 40°C (exothermic reaction). The mixture was stirred for further 4 h at 40°C to 45°C. Then the reaction mixture was poured into 3 l of ice-water and extracted for times with 1 l each of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and the ethyl acetate removed in a rotary evaporator at reduced pressure. 503 g of an oil were obtained. The crude product was used directly in the next reaction step.

b) 4-Benzyloxycarbonylcinnamic acid

245 g (2.4 mol) of malonic acid were dissolved in 360 ml of pyridine (exothermic, temperature raised to about 50°C). Then 503 g of the crude benzyl 4-formylbenzoate

obtained in step a) and 20 ml of piperidine were added, and the mixture was heated to reflux until the production of carbon dioxide had ceased (about 7 h). The mixture was cooled to room temperature, then 2 l of water were added and the product was precipitated by acidification of the stirred mixture with ca. 600 ml of concentrated hydrochloric acid to pH 1.8 at 10°C. The precipitated product was filtered off, washed with water and dried at 50°C under reduced pressure. Combined yield of step a) and step b): 529.1 g (97 %).

MS (CI): 283.2 $(M+H)^+$

$^1$H-NMR (DMSO-$D_6$): δ (ppm) = 12.58 (s, broad, 1H); 8.02 (d, 2H); 7.85 (d, 2H); 7.65 (d, 1H); 7.55 - 7.30 (m, 5H); 6.70 (d, 1H); 5.38 (s, 2H)

2) Benzyl 4-(2-(pyrimidin-2-ylcarbamoyl)vinyl)benzoate

282.3 g (1 mol) of 4-benzyloxycarbonylcinnamic acid were suspended in 2 l of toluene and 108 ml (1.48 mol) of thionyl chloride were added. The mixture was reacted for about 7 h until the production of sulfur dioxide had ceased and a clear solution of the acid chloride was obtained. The solvent was removed under reduced pressure in a rotary evaporator. The residue was dissolved in 1 l of dichloromethane and added dropwise during 1 h to a solution of 95.2 g (1 mol) of 2-aminopyrimidine and 81 ml (1 mol) of pyridine in 2 l of dichloromethane at 0°C to 5°C. The reaction mixture was stirred for 1 h at room temperature and then evaporated under reduced pressure in a rotary evaporator. The residue was dissolved in 2.5 l of hot ethanol, then 1.5 l of water were added and the mixture was cooled slowly to 0°C to 5°C whereupon the product precipitated. The product was filtered, washed with water and dried at 60°C under reduced pressure. Yield: 317.1 g (88 %)

MS (ES): 360.2 $(M+H)^+$

$^1$H-NMR (DMSO-$D_6$): δ (ppm) = 10.85 (s, broad, 1H); 8.72 (s, 1H); 8.68 (s, 1H); 8.02 (d, 2H); 7.85 (d, 2H); 7,65 (d, 1H); 7.55 - 7.18 (m, 7H); 5.38 (s, 2H)

3) 4-(2-(1,4,5,6-Tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid

305 g (0.85 mol) of benzyl 4-(2-(pyrimidin-2-ylcarbamoyl)vinyl)benzoate were hydrogenated in a 20 l Büchi autoclave in 8 l of 20% aqueous acetic acid in the presence of 25 g of 10% palladium/charcoal at 40°C under a hydrogen pressure of 2 bar. After 6 h and uptake of 65.76 l of hydrogen the reaction was finished. After standing overnight the mixture was warmed to 70°C and the catalyst filtered off. The autoclave was washed with 3 l of 20% aqueous acetic acid at 70°C. The catalyst was washed with 1.5 l of 20% aqueous acetic acid at 70°C. The filtrate was evaporated under reduced pressure in a rotary evaporator and the residue was dissolved in 1 l of water with heating. Upon cooling to room temperature the product precipitated. The mixture was cooled to 0°C to 5°C, the product was filtered off, washed with cold water and dried under reduced pressure at 50°C. Yield: 212 g (90.6 %)

MS (ES): 276.1 $(M+H)^+$

$^1$H-NMR (trifluoroacetic acid): δ (ppm) = 11.55 (s); 8.15 (d, 2H); 7.40 (d, 2H); 3.62 (dd, 4H); 3.18 (dd, 2H); 2.95 (dd, 2H); 2.15 (m, 2H)

4) 4-(2-(1,4,5,6-Tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoyl chloride hydrochloride

110.2 g (0.4 mol) of 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid were suspended in 1.5 l of toluene, then 35 ml of thionyl chloride were added and the mixture was heated to 70°C for 2 h. Then further 16 ml of thionyl chloride were added and heating was continued until the evolution of sulfur dioxide had ceased. The almost clear solution was evaporated to dryness to give 139.5 g of the crude title compound as a yellow powder. This product was directly used in the subsequent reaction.

MS (FAB): 294.1 ($(M+H)^+$ of the free base)

$^1$H-NMR ($CDCl_3$): δ (ppm) = 13.05 (s, broad, 1H); 9.35 (s, broad, 2H); 8.05 (d, 2H); 7.40 (d, 2H); 3.50 (m, 4H); 3.10 (dd, 2H); 2.95 (dd, 2H); 2.05 (m, 2H)

5) (2S)-3-Carbamoyl-2-(naphthalene-1-sulfonylamino)propionic acid

132.12 g (1 mol) of (S)-asparagine were dissolved in a mixture of 800 ml of water and 500 ml of 2 N sodium hydroxide. Then 500 ml of tetrahydrofuran were added. The mixture was cooled to 0°C, and while keeping the pH at 12.0 - 12.5 with 2 N sodium hydroxide a solution of 226.7 g (1 mol) of naphthalene-1-sulfonyl chloride in 500 ml of tetrahydrofuran was added within 1 h. The mixture was stirred for 1 h at 0°C while maintaining the pH at 12.5. Then the mixture was allowed to warm to room temperature, stirred for further 2 h and left at room temperature overnight. The pH was adjusted to about 7 with concentrated hydrochloric acid and the tetrahydrofuran was removed in vakuum in a rotary evaporator. The remaining aqueous solution was cooled to 0°C and with stirring acidified to pH 1.8 by addition of concentrated hydrochloric acid. After stirring for 30 min at 0°C the precipitated product was filtered off, washed with water and dried in vacuo at 40°C. Yield: 240 g (75 %)

MS (ES): 323.1 $(M+H)^+$

$^1$H-NMR (DMSO-$D_6$): δ (ppm) = 12.50 (s, 1H); 8.65 (d, 1H); 8.35 (d, 1H); 8.20 (d, 1H); 8.17 (d, 1H); 8.09 (d, 1H); 7.80 - 7.60 (m, 3H); 7.28 (s, 1H); 6.82 (s, 1H); 4.15 (m, 1H); 2.45 (dd, 1H); 2.23 (dd, 1H)

6) (2S)-3-Amino-2-(naphthalene-1-sulfonylamino)propionic acid

To a stirred solution of 148 g (4.1 mol) of sodium hydroxide in 940 ml of water 26 ml (0.5 mol) of bromine were added over 45 min at 0°C. Then, separately, 129 g (0.4 mol) of (2S)-3-carbamoyl-2-(naphthalene-1-sulfonylamino)succinic acid were dissolved in 400 ml of 2 N sodium hydroxide and further 16 g of sodium hydroxide were added. This solution was cooled to 5°C and added with vigorous stirring to the previously prepared sodium hypobromite solution while maintaining the temperature of the reaction mixture below 10°C. The mixture was stirred for further 15 min at 10°C and then warmed within 30 min to 45°C. Then heating was removed and an exothermic reaction proceeded for about 1 h with a peak temperature of about 50°C. When the exothermic reaction had ceased the mixture was heated within 20 min to 70°C and maintained at this temperature for 10 min. Then the reaction mixture was cooled to 40°C and at this temperature acidified to pH 6.8 with 330 ml of

overnight at room temperature, the mixture was cooled to 10°C, the product filtered off, washed with water and dried in vacuuo. Yield: 97.7 g (83 %).

MS (FAB): 295.0 $(M+H)^+$

$^1$H-NMR (DMSO-$D_6$): δ (ppm) = 8.58 (d, 1H); 8.25 (d, 2H); 8.09 (d, 1H); 7.90 (s, very broad, 3H); 7.80 - 7.60 (m, 3H); 3.35 (s, very broad, 2H); 3.18 (m, 1H); 3.05 (dd, 1H); 2.82 (dd, 1H)

7) Ethyl (2S)-3-amino-2-(naphthalene-1-sulfonylamino)propionate hydrochloride

147.2 g (0.5 mol) of (2S)-3-amino-2-(naphthalene-1-sulfonylamino)propionic acid were suspended in 1 l of ethanol and hydrogen chloride gas was introduced into the mixture for about 2 h whereupon the temperature increased to about 35°C and a clear solution was obtained. Then the mixture was evaporated in vacuo in a rotary evaporator. The residue was dissolved in hot ethanol and diisopropyl ether was added until precipitation of the product started.The product was allowed to crystallize overnight at room temperature. The title hydrochloride was filtered off, washed with diisopropyl ether and dried in vacuo. Yield: 148 g (83 %).

MS (ES): 323.2 ($(M+H)^+$ of the free base)

$^1$H-NMR (DMSO-$D_6$): δ (ppm) = 8.95 (s, broad, 1H); 8.63 (d, 1H); 8.40 - 8.20 (m, 3H); 8.13 (d, 1H); 8.09 (d, 1H); 7.80 - 7.60 (m, 3H); 4.12 (m, 1H); 3.50 - 3.36 (m, 2H); 3.08 (dd, 1H); 2.92 (dd, 1H); 0.55 (t, 3H)

8) Ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate hemifumarate

25.1 g (0.07 mol) of ethyl (2S)-3-amino-2-(naphthalene-1-sulfonylamino)propionate hydrochloride were dissolved in 100 ml of dichloromethane by addition of 17.7 g (0.21 mol) of sodium bicarbonate in 30 ml water. Then under vigourous stirring 23.2 g (0.07 mol) of 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoyl chloride hydrochloride were added in portions within 30 min. The reaction mixture was stirred for further 1 h and then the layers were separated. The organic layer was extracted

sulfate was filtered off and washed with dichloromethane. The filtrate was concentrated to about 100 ml and 4.1 g (0.035 mol) of fumaric acid were added to the obtained dichloromethane solution of ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate. The mixture was heated to reflux until a clear solution was obtained. Upon cooling the title hemifumarate started to precipitate. Precipitation was completed by addition of 300 ml ethyl acetate. The product was collected by filtration, washed with ethyl acetate and dried. Yield: 35.5 g (79.5%). Melting point 201°C.

MS (FAB): 580.3 ($(M+H)^+$ of the free base)

$^1$H-NMR (DMSO-$D_6$): δ (ppm) = 9.73 (s, broad, 1H); 8.8 (s, very broad, 1H); 8.63 (d, 1H); 8.33 (t, 1H); 8.16 (d, 1H); 8.09 (d, 1H); 8.01 (d, 1H); 7.72 - 7.50 (m, 5H); 7.24 (d, 2H); 6.50 (s, 1H); 4.08 (t, 1H); 3.66 - 3.45 (m, 4H); 3.34 (q, 2H); 3.27 (t, 4H); 2.88 (dd, 2H); 2.59 (dd, 2H); 1.79 (m, 2H); 0.79 (t, 3H)

9) Pharmacological testing: PTH-induced hypercalcemia in the TPTX rat model of bone resorption

In this in vivo model a stimulation of bone resorption is induced in thyroparathyroidectomized (TPTX) rats by the infusion of parathyroid hormone (PTH). The changes in bone resorption are monitored by measuring the serum calcium concentration which is directly related to the extent of bone resorption.

Male Sprague Dawley rats (OFA-IFFA CREDO, France) weighting 150 - 200 g were thyroparathyroidectomized by the supplier. The rats were allowed free access to a standard commercial pelleted diet containing 7 g Ca/kg (UAR) and Eau de Volvic water. The success of thyroparathyroidectomy was tested by measuring serum calcium concentrations 8 days after operation in overnight fasted animals. Rats were considered as TPTX when the serum calcium level was < 80 mg/l.

For treatment with PTH, rat PTH(1-34) (Bachem) was dissolved in 0.15 M sodium chloride solution containing 2 % Cys-HCl and delivered via osmotic minipumps were inserted into the

intraperitoneal cavities under ketamin (75 mg/kg) and acepromazin (2.5 mg/kg) anesthesia in overnight fasted TPTX rats. In the control group TPTX rats received minipumps filled with the vehicle of PTH.

To determine the effect of the compound of formula I, PTH treated TPTX rats were administered twice 10 mg/kg of this compound perorally at time 0 and 3 h after the start of PTH infusion (compound group). In the same manner PTH treated TPTX rats were administered the vehicle (PTH group), and TPTX rats not treated with PTH were administered the vehicle (control group). The experiment was performed for a total of 6 hours. At the end of the treatment protocol, whole blood was collected after decapitation. The blood samples were centrifugated at 3000 rpm for 15 min (CR422 Jouan) to obtain serum.

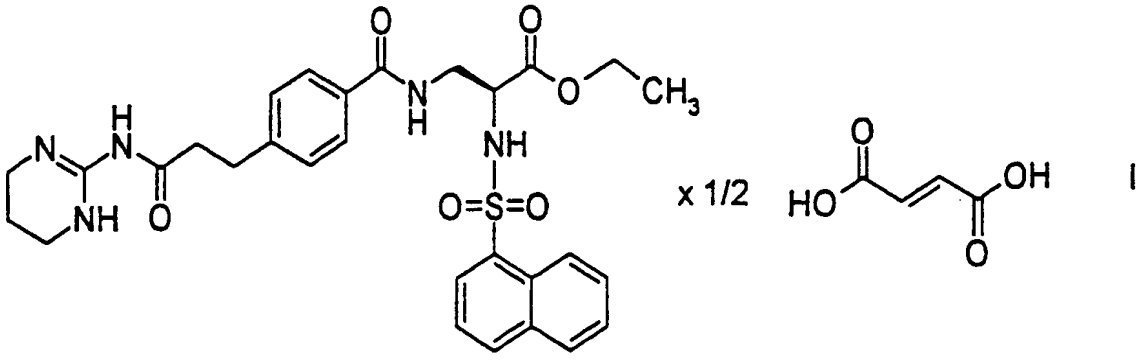
Serum total calcium concentrations (= calcemia) were measured colorimetrically (Ciba-Corning) using a IEMS Labsystems microplate reader at 540 nm. The differences between the mean values of calcemia in the groups were analysed for variance and by Dunnett's test. The activity of the test compound was calculated as % effect according to the formula:

$$\% \text{ effect} = \frac{\text{Calcemia}_{(\text{compound group})} - \text{Calcemia}_{(\text{PTH group})}}{\text{Calcemia}_{(\text{PTH group})} - \text{Calcemia}_{(\text{control group})}} \times 100$$

The % effect observed with the compound of formula I administered perorally twice at 10 mg/kg was -45 %. This in vivo result shows that the compound of formula I is a highly efficient inhibitor of bone resorption.

Patent claims

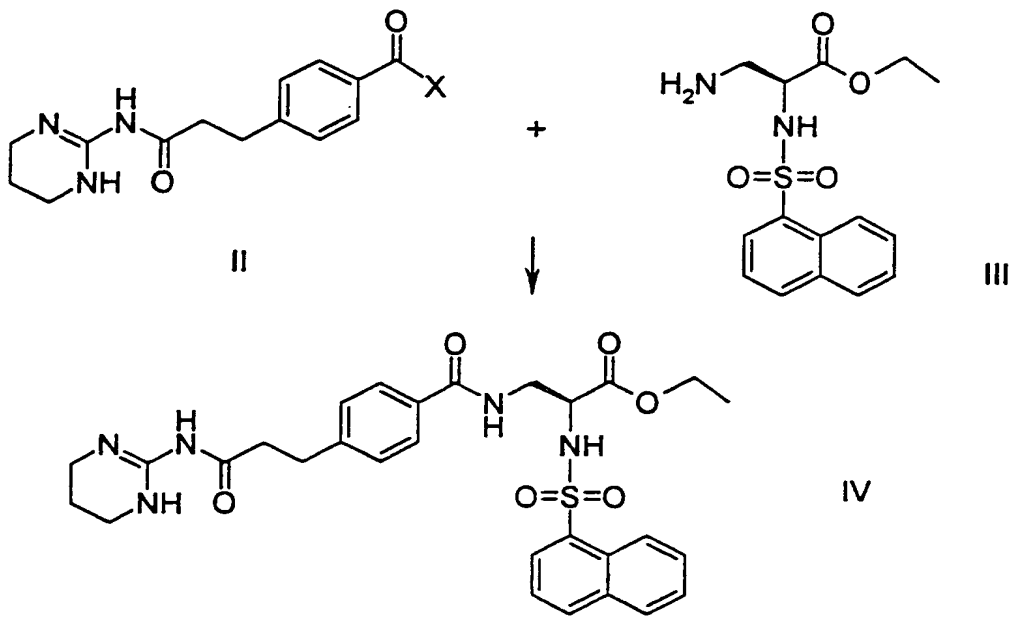
1. Ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate hemifumarate of the formula I.



I

2. A pharmaceutical composition, comprising the compound of the formula I as claimed in claim 1 and a pharmaceutically acceptable carrier.

3. A process for the preparation of ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate of the formula IV or a salt thereof, comprising reacting 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid or a derivative thereof of the formula II wherein X is hydroxy or a leaving group, and ethyl (2S)-3-amino-2-(naphthalene-1-sulfonylamino)propionate of the formula III, or a salt or salts of any one or both of these compounds.



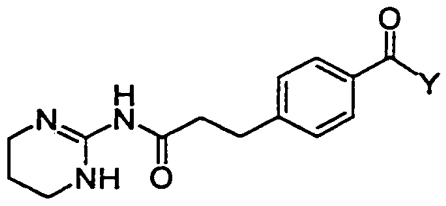
II + III → IV

4. The process as claimed in claim 3, characterized in that X is Cl.

5. The process as claimed in claims 3 and/or 4, characterized in that subsequently to the reaction of the compounds of the formulae II and III an acid is employed and an acid addition salt of the compound of formula IV with said acid is prepared.

6. The process as claimed in one or more of claims 3 to 5, characterized in that ethyl (2S)-2-(naphthalene-1-sulfonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionate hemifumarate is prepared.

7. A compound of the formula XV,

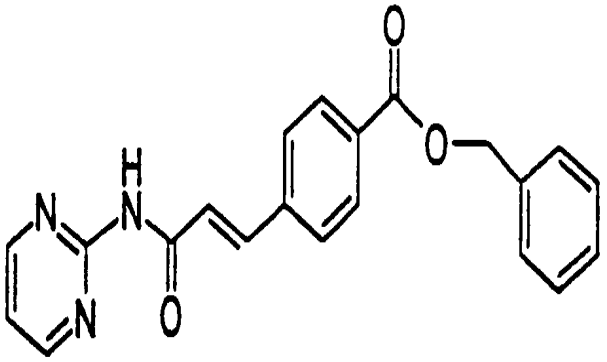


XV

wherein Y is hydroxy, chlorine or bromine, or a salt thereof.

8. A compound of the formula XV as claimed in claim 7 which is 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid or 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoyl chloride or a salt of any of these compounds.

9. Benzyl 4-(2-(pyrimidin-2-ylcarbamoyl)vinyl)benzoate of the formula XIII or a salt thereof.



XIII

10. A process for the preparation of 4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoic acid or a salt thereof, comprising hydrogenating benzyl 4-(2-(pyrimidin-2-ylcarbamoyl)vinyl)benzoate or a salt thereof

# INTERNATIONAL SEARCH REPORT

Inte[redacted]Application No
PCT/EP 00/06504

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/16 A61K31/505 C07D239/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 October 2000 | 02/11/2000 |

| Name and mailing address of the ISA | Authorized officer |
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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Gettins, M |

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